



King's Research Portal

DOI:

[10.3899/jrheum.160818](https://doi.org/10.3899/jrheum.160818)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Filkova, M., Carvalho, J., Norton, S., Scott, D., Mant, T., Molokhia, M., Cope, A., & Galloway, J. (2017). Polypharmacy and unplanned hospitalizations in patients with rheumatoid arthritis. *Journal of Rheumatology*, 44(12), 1786-1793. <https://doi.org/10.3899/jrheum.160818>

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Polypharmacy and unplanned hospitalizations in patients with rheumatoid arthritis

Maria Filkova^{1, 2}, João Carvalho^{1, 3}, Sam Norton⁴, David Scott¹, Tim Mant⁵, Mariam Molokhia⁶, Andrew Cope¹, James Galloway^{1*}

¹Academic Department of Rheumatology, King's College London, London, UK; ²Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, ³Centro Hospitalar de Setúbal E.P.E. - Hospital de São Bernardo, Setúbal, Portugal, ⁴Department of Psychology, King's College London, London, UK; ⁵Quintiles Drug Research Unit at Guy's Hospital, London, UK; ⁶ Division of Health and Social Care Research, King's College London, London, UK

Highest academic degrees of all authors: M Filkova: MD PhD; J Carvalho: MD; S Norton: BSc, MSc, PhD ; D Scott: Prof. MD FRCP ; T Mant: Prof. MD, MBBS, FRCP, FFPM; M Molokhia: BSc MBChB MRCP, MSc, PhD; A Cope: Prof. BSc, PhD, FRCP, FHEA; J Galloway: MBChB, MRCP, MSc, PhD

* Corresponding author:

James Galloway, MBChB, MRCP, MSc, PhD

Academic Department of Rheumatology, Weston Education Centre, King's College London,

Cutcombe Road

SE5 9RJ London

Telephone: +44 (0) 20 3299 7772

Email: james.galloway@kcl.ac.uk

Running title: Polypharmacy in rheumatoid arthritis

This study was supported by an Arthritis Research UK Experimental Arthritis Treatment Centre grant and project of the MHCR for conceptual research development No. 023728.

Abstract

Objective: Polypharmacy, the prescribing of multiple drugs for an individual, is rising in prevalence. Polypharmacy associates with an increased risk of adverse drug reactions (ADR) and hospital admissions. We investigated the relationship between polypharmacy, characteristics of rheumatoid arthritis (RA) and the risk of unplanned hospital admissions.

Methods: Patients from a hospital RA cohort were retrospectively analysed. Information was captured via electronic medical records. Cox proportional hazards were used to compare hospitalization risk according to levels of polypharmacy. Admissions were adjudicated to determine whether an ADR was implicated.

Results: 1,101 patients were studied; the mean number of all medications was 5. Polypharmacy correlated with increasing age, disease duration, disease activity and disability. 16% patients had at least one unplanned admission. Patients on ≥ 10 medications had an adjusted hazard ratio for hospitalisation of 3.1 (95%CI 2.1-4.5), compared to those taking 0-5 medications. Corticosteroid use associated with a doubling in adjusted risk of admission 1.7 (95%CI 1.2-2.4). The most common reason for hospitalisation was infection (28%). Whilst in half of all admissions an ADR was a possible contributing factor, only 2% admissions were attributed as a direct result of an ADR.

Conclusion: Polypharmacy is common in RA and is a prognostic marker associated with increased risk of acute hospitalizations. Our data suggest that polypharmacy may be an indicator of comorbidity burden rather than a contributing cause of a drug-related toxicity. Polypharmacy should be monitored to minimize inappropriate combination of prescribed medications. Polypharmacy may be a useful predictor of clinical outcomes in epidemiologic studies.

Key words: polypharmacy, hospitalization, rheumatoid arthritis

Introduction

Prescribing is the commonest NHS intervention and the second highest level of spending after staffing costs. Polypharmacy, the prescribing of multiple drugs for an individual, is rising in prevalence in the UK. A population based study of 300,000 patients revealed the mean number of prescribed medication increased from 3.3 in 1995 to 4.4 in 2010. This corresponded with an increase in the proportion of patients receiving 5 or more drugs climbing from 12 to 22%, and those receiving 10 or more drugs increased from 2 to 6% (1). The reason for growing levels of polypharmacy include an ageing population combined with guideline-driven management that results in patients receiving multiple concurrent medications for several conditions. Polypharmacy has substantial relevance in rheumatoid arthritis (RA). Treharne reviewed case notes for 348 patients with RA, documenting high levels of polypharmacy (mean medication count 5.4), which in turn associated with comorbid diagnoses and increasing disease duration (2).

Clinical guidelines in RA, focused on intensive treatment regimens with disease modifying drugs (DMARD) and biologics, improve RA outcomes but, of necessity, increase polypharmacy. In addition, patients with RA have a higher burden of comorbidity than the general population, which in turn correlates with high mortality (3, 4). Therefore, there is an increasing need for screening and management of comorbidities in RA (5) that would contribute to higher rates of polypharmacy. Explanations for the increasing prevalence of comorbidities include factors directly related to the diagnosis of RA (e.g. cardiovascular disease) or shared risk factors (e.g. smoking) (6-9).

Previous population studies have demonstrated that PP associates with an increased risk of adverse drug reactions (ADR), reduced medication adherence, and increased hospital admissions (10). For example ADRs are prevalent, one study estimated that 6.5% of acute medical admissions in two North-West UK hospitals were due to ADRs (11). A UK national survey of ADR related hospital admissions

suggested the number of ADR admissions has increased disproportionately to the total hospital admissions. The increase of emergency admissions with a primary diagnosis of an ADR increased by 37% over 10 years, certainly some may be due to improved diagnoses (12). However, in-hospital mortality due to ADR admissions had also increased during the same period (12). In a study of the general US population, ADRs were shown to be responsible for 4.7% of all admissions (13).

Although many studies have reported on comorbidities in RA, there are few studies specifically examining PP in an RA population (2). Given that the advent of combination disease modifying therapy that actively increases medication burden, understanding PP is of particular importance in RA. Here, we set out to (1) evaluate the relationship between PP, RA disease characteristics and the risk of unplanned hospital admission; and (2) to explore the causal relationship between PP and hospitalisation risk.

Methods

Participants, data source and polypharmacy measures

Data from an inner city London secondary care cohort of RA patients were used. RA patients met 1987 ACR or 2010 ACR/EULAR criteria for the diagnosis of RA (14, 15). The design was a retrospective cohort study. In order to provide contemporary data, an 18-month window of follow up was selected commencing in May 2013. The hospital uses an electronic patient record for both inpatient and outpatient care, with all patient encounters recorded in a structured database. Information from all patients registered at the hospital with a consultant diagnosis of RA and under active follow up were analysed. Patient baseline characteristics were extracted from their most recent clinic visit prior to the start of follow up period including disease activity score (DAS28), disability score (Health Assessment Questionnaire, HAQ) and full list of medications (Table 1). The median time between the baseline visit and 1st May 2013 was 12 months (interquartile range 8-15).

Polypharmacy information was extracted from outpatient medication charts that are updated by physicians at each hospital visit. Medications were sorted according to target organ/system with sub-categories according to mode of action: drugs specific for treatment of RA (DMARD, biologic treatment, oral corticosteroids), cardiovascular, non-steroid anti-inflammatory drugs, opioid-based analgesia and/or paracetamol, respiratory, gastrointestinal, central nervous system affecting drugs, medication for treatment of diabetes mellitus, lipid/cholesterol lowering drugs, anti-platelets/anticoagulants, dietary supplements (including calcium and vitamin D except herbal supplements), and others (e.g. antibiotics/anti-mycotic/anti-parasitic/anti-viral drugs, hormonal treatment, antihistamines). Each patient was assigned a PP level at baseline based upon the total number of prescribed medication (including DMARDs) but dietary supplements were excluded from further statistical analyses.

Acute hospitalizations and review criteria

All acute admissions to the hospital during follow up were identified from the coded submissions to Hospital Episode Statistics, the central reporting system in England and Wales. Data on admissions to other hospitals were not available. Since a key aim of this study was to attempt to identify what proportion of hospitalisations were attributable to PP, as opposed to the underlying disease, detailed review of every first admission was undertaken.

Unlike the baseline drug chart, the admission medication list was drawn directly from the primary care record and verified by the hospital pharmacist. The full electronic records for each admission (admission and discharge summary, clinical notes, medication records, laboratory results) were then independently reviewed by two clinicians: MF (rheumatology and clinical pharmacology) and JC (general internal medicine). The data were reviewed to adjudicate admission diagnosis, presence of an ADR, drug-drug interactions, and also whether the ADR was avoidable. Assessments were based on previously validated approaches (16-18).

Adverse drug reaction

An ADR is defined as any undesirable, appreciably harmful/unpleasant reaction related to the use of a drug which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen or withdrawal of the product (16). Attribution of an admission to an ADR was categorised as definite/probable/possible/unlikely, in line with previously published assessment methods (16) (Supplementary appendix 1). The involvement of RA-related drugs in ADR across all categories was assessed (Supplementary appendix 2). Assessment of ADR and drug-drug interactions was guided by the STOPP criteria (19) and Beers criteria (17).

Drug-drug interactions

It is important to separate/differentiate an ADR from a drug-drug pharmacological interaction, which in itself does not necessarily cause clinical harm. Drug-drug interactions were evaluated based on pharmaceutical, pharmacodynamic or pharmacokinetic mechanism. Clinical relevance of any observed interaction was graded as major, moderate or none as published before (18) (Supplementary appendix 3).

Avoidability

Avoidability of ADR related admission was classified as definitely avoidable, possibly avoidable, or unavoidable, also using previously published criteria (11, 20) (Supplementary appendix 4).

Ethics

This study was undertaken as part of a locally approved service evaluation using existing data collected through routine care. All data were reviewed and analysed by clinicians working within the

department. In accordance with the Governance Arrangements for Research Ethics Committees in the United Kingdom, external ethics approval was not required.

Statistical analysis

Baseline characteristics were compared across groups using Kruskal-Wallis (for continuous variables) or Chi squared (for dichotomous variables) tests. Correlations were calculated using Spearman's correlation coefficient. Risk of hospitalisation was compared between PP strata using Cox proportional hazards regression. Tests of the proportional hazards assumption were carried out with Schoenfeld residuals derived from the final models. Follow up was censored at date of first admission or study end, whichever came first. A model incorporating a restricted cubic spline for PP level was constructed to describe graphically the non-linear association between hospitalisation risk with number of prescribed medications. PP levels (0-5, 6-9 or ≥ 10 medications) were defined prior analysis based upon standardised cutoffs in the literature (1, 21, 22). The analysis was performed using Stata13 and GraphPad Prism 5.

Results

Prescribing strategy and association of PP with disease characteristics

The study included 1,101 patients with an established diagnosis of RA, with a mean DAS28 of 3.6 ± 1.6 , a mean HAQ of 1.3 ± 0.9 and disease duration of 10 years (Table 1). Overall the mean number of prescribed medications was 5.2 ± 3.3 , 60% of patients had ≤ 5 medications and 11% of patients had ≥ 10 medications. In total 79% of patients were receiving DMARDs, while 22% were receiving biologics. Out of all patients, 45% were on DMARD monotherapy, 26% were on dual and 7% on triple combination DMARD therapy, 16% were receiving corticosteroids (Table 1). Excluding RA treatment the mean number of medications was 3.8 ± 3.3 ; the most common prescribed therapies included treatment for cardiovascular diseases (38% of all patients, comprising: calcium channel blockers 25%, diuretics 24%,

α/β adrenergic blocking agents 17%, angiotensin II receptor antagonists 13%, angiotensin converting enzyme inhibitors 6%, others 15%), opioid-based analgesia (34%) and non-steroid anti-inflammatory drugs (32%) (Supplementary figure 1a).

Polypharmacy increased with age ($r=0.26$, $p<0.001$), with 8% of patients <65 on ≥ 10 medications, in contrast to 16% of patients >65 . Women had a higher mean number of medications (females 5.3 vs. males 4.9, $p=0.01$). There appeared to be an inverse relationship between smoking and PP, with the proportion of current smokers declining with increasing numbers of medication (mean number of medications in non-smokers 5.6 ± 3.2 ; smokers 4.8 ± 2.9 , $p=0.0084$).

Measures of RA disease severity were significantly correlated with PP, with increasing PP corresponding to higher DAS28 ($r=0.26$, $p<0.001$), greater HAQ scores ($r=0.45$, $p<0.001$), and longer disease duration ($r=0.14$, $p<0.001$) (Figure 1).

Hospitalisations

The most common reason for hospitalization was infection (28.9%), which was not significantly different across PP strata ($p=0.24$). The most common were respiratory tract infections (15.9%), urinary tract infections (6.4%) and others (including 2 cases of septic arthritis). Neurologic conditions were responsible for 13%, trauma for 10%, cardiovascular complications for 8 % of admissions. Rheumatoid flare was implicated in only 5.8% of all acute admission. Other causes are provided in Supplementary figure 1b.

Polypharmacy as a predictor of acute hospitalizations

During the 18-month follow up window there were 303 admissions amongst 173 patients (incidence 10.8/100 patient years, 95% confidence interval (CI) 9.3-12.6). Of the 173 patients who were admitted,

63 (35%) had repeated admissions during follow up. Further analysis below only included data on first admissions (n=173).

There was a non-linear association between increasing polypharmacy and more frequent acute hospitalisations, with an indication that the likelihood of being admitted to hospital increases sharply in patients prescribed ≥ 10 medications (Figure 2). Patients on ≥ 10 medications age and gender adjusted hazard ratio (HR) for first hospitalisation was 3.1 (95% CI 2.1-4.5) compared to those on ≤ 5 medications. Patients on 6-9 medications were not at significantly higher risk compared to those on ≤ 5 medications (HR 1.0, 95% CI 0.7-1.5) (Table 2).

DMARD combination strategies were not associated with increased hospitalisation risk (age and gender adjusted HR for DMARD monotherapy 0.8 (95% CI 0.6-1.1), dual therapy HR 1.1 (95% CI 0.7-1.5), triple therapy HR 0.8 (95% CI 0.4-1.5). Biologic therapy did not relate to an increased risk of hospitalization (age and gender adjusted HR 0.8 (95% CI 0.5-1.3). However, use of corticosteroids was associated with a doubling in risk (HR 2.3, 95% CI 1.6-3.1) of admission (Supplementary table 1). The association between corticosteroid and admission remained significant after adjusting for polypharmacy, age and gender (HR 1.7, 95% CI 1.2-2.4).

Adverse drug reactions

Overall, 12 admissions (6.9% of all admissions) were considered “definitely” or “probably” attributable to an ADR (Table 3). The definite and probably ADRs were distributed across all PP strata (Table 4). In half of these ADRs, an RA medication was implicated in the ADR (Table 3, Supplementary table 2).

A substantial proportion (44.5%) of admissions were coded as “possibly” attributable to an ADR. Amongst the possibly attributable ADRs, 40/77 (51.9%) involved an RA drug. The nature of ADR classification means that completely excluding an ADR for an admission can be difficult (e.g. if a patient receiving DMARDs is admitted due to infection).

In terms of which RA drugs were involved in ADRs, 17.4% involved corticosteroids, 69.6% DMARDs and 26.1% biologics. Involvement of RA treatments in ADR related admissions across PP strata is shown in Table 4.

Drug-drug interactions and avoidability of ADR-related admissions

Drug-drug interactions contributed to 10 out of 173 (11.2%) of admissions. Of these, 2 were definitely, 3 probably and 5 possibly linked to acute admissions (Table 3). Both definite major drug-drug interactions involved anticoagulants. DMARDs contributed to 4 (1 definitely involved in ADR related admission), and biologics to 2 major drug-drug interactions. Drug-drug interactions were more frequent in patients in higher PP strata (Table 4).

After adjudication, only 2 (4.5%) of ADR related hospitalizations were deemed definitely avoidable from a prescribing perspective; both involved predictable drug interactions with anticoagulants (Table 3).

Discussion

This is the first study analyzing the association between PP and hospitalisation specifically in RA patients. Similarly, while data on ADRs as a cause of admissions are available for the general population (11, 12, 23-25) the data in RA patients are missing.

It is difficult to estimate the prevalence of PP in general population given different definitions of PP and study population analyzed (primary/secondary care, hospital admissions, elderly population, comorbidity burden etc.). A recent study using primary care data from general population showed that almost 50% of patients aged >20 years admitted to the hospital were prescribed at least one regular medication, with 25.2% receiving 1-3, 16.9% receiving 4-9 and 4.6% receiving ≥ 10 medications (26).

Increasing numbers of regular medications are seen with female gender, older age, greater socioeconomic deprivation and increasing multimorbidity, cardiometabolic conditions being the most important disease cluster (22, 26). We observed that polypharmacy is common in patients with RA and is more frequently observed in women, patients with higher disease activity, higher levels of functional impairment and longer disease duration. None of these observations is unexpected, however the absolute numbers of patients receiving polypharmacy is high, especially in the elderly.

Patients with higher levels of polypharmacy had a substantially greater risk of unplanned hospitalization. The risk of hospitalisation was more marked in patients receiving >10 medications. The observation that the polypharmacy and hospitalisation risk was non-linear is particularly relevant if one were to attempt to use polypharmacy as an epidemiological surrogate for comorbidity. However, at a patient level, it is important to consider why the pattern is observed. It may be that the relationship between PP and comorbidity becomes stronger above a certain point, especially since we included DMARDs in the total medication count.

In addition to the relationship with comorbidity, PP may be a direct causal factor in hospitalisation through ADRs. It has previously been shown that ADRs account for between 0.5 and 6.5% of admissions [10, 11, 22]. Our estimate of definite or probable ADR related admissions within an RA cohort was 6.9%. The low absolute numbers of definite or probable ADR precluded detailed analysis, however it appeared that ADRs were linked to specific classes of high risk drugs (e.g. anticoagulants), whose effects may be potentiated by specific co-morbidities and drug interactions which increase bleeding risk, rather than absolute numbers of medication.

Some ADRs can be avoidable (hazardous prescribing), however we observed very few such events. In contrast, many ADRs occur in the setting of appropriate prescribing. In the context of RA, most clinicians now accept that the infectious risks of DMARDs are far outweighed by the beneficial effect upon the RA, with the knowledge that untreated RA is a far more hazardous state.

Our analyses, with specific consideration for RA drugs within the context of polypharmacy, were reassuring, with demonstrated no apparent association between more intensive DMARD strategies, including use of biologics, and hospitalisation risk. There was however a two-fold higher rate of hospitalisation amongst corticosteroids users. These could have been prescribed either for treatment of RA or another comorbidity increasing the risk of hospitalization, however, due to lack of information on comorbidities in our study we are unable to make conclusions on an indication. Although DMARDs contribute to PP it may be that an adequate control of disease activity is protective against admission. An alternative explanation is that there may be channelling bias, with healthier patients more likely to be prescribed combination DMARD or biologic treatment strategies, whilst clinicians adopt more cautious approaches (perhaps favouring steroids) in patients with complex background comorbidity.

Drug-drug interactions were documented in 82% of admissions, but only 11% were considered of clinical significance. As expected, patients in higher PP strata were more exposed to drug-drug interactions compared to patients in the lowest strata. However, it is important to acknowledge that simple assessments of drug-drug interaction may dramatically overestimate risk of clinically relevant problems (27).

PP may be a useful proxy tool (unlike the calculation of indices of comorbidity) to adjust for confounding by co-morbidity in epidemiologic analyses and identify patients at high risk of hospitalizations for targeted risk management. Comorbidity indices have been used to measure and weigh the overall burden of comorbidities and have been used in predicting mortality (28) but not in predicting the acute admissions. Different methods have been used to predict risk of emergency admissions, which involved demographic, lifestyle, laboratory variables, clinical values and chronic disease into account (23, 29). These tools appear complicated for stratification of acute admissions in daily practice and routinely captured PP data may act as a useful surrogate. Whether this is the case, it could be investigated in further studies.

A key strength of this research is the use of real world data - electronic medical records (EMR) and emphasis on collecting defined core data generated in day-to-day situations rather than typically selective controlled trials. The growing use of EMR and emphasis on collecting defined core data in specific diseases like RA makes it easier to use real-world data sources in research. Using routinely collected data to evaluate the impact of PP has both strengths and limitations. The growing use of EMR and routine data sources may help overcome the some issues of generalizability that limits trials.

Limitations of our study include misclassification biases, unmeasured confounding, missing data and censorship. Clinicians may be less thorough in recording medication in routine care than in formal clinical studies, resulting in reduced data quality or missing data. As we relied upon the secondary care record of patient prescribed medication, it is likely that we were unaware of some medications patients are receiving (including OTC medications), and our measurement of PP is likely an underestimate. However, for all hospitalisations a pharmacist undertakes medicines reconciliation directly with primary care and therefore we were able to compare an actual number of prescribed medications with our own record of PP at baseline. Amongst patients admitted with an infection, the mean number of medications recorded in our baseline record was 7.0 (SD 4.0), compared to a mean number of medications of 8.9 (SD 4.3) at the time of admission. Whilst some of this increase may genuinely represent additional medications prescribed between baseline and the date of admission, it also provides some estimate of the extent of missing information on baseline medication.

With regard to misclassification of exposure, recall bias was avoided by using electronically captured prescription data but precise information on dispensing and adherence was unavailable. Indeed, it was inaccuracy in comorbidity coding that initiated the authors' interest in polypharmacy as a measure. It is notable that when we compared the medicines reconciliation data from pharmacists at the time of admission, the extent of medication misclassification was reassuringly low. However, a number of nuances, such as transient episodic use of medications, may have been missed. A further limitation is that it is likely that some patients had admissions at other hospitals. We hypothesize that additional admission to other inner-city Trust hospitals may have contributed to the higher number of drug-

related admissions. Therefore our estimates of hospitalisation rate can be considered as conservative as we will have underestimated the true rate. However, there is no reason to think that this bias would have impacted upon patients at different levels of PP differentially. We attempted to reduce confounding by design and analysis (multivariable adjustments on age and gender), however residual confounding likely remains (e.g. socioeconomic and other factors). The complexity of medications in some cases and the lack of full medical records made the judgement of appropriate or inappropriate prescribing impossible.

In conclusion, our study found PP to be associated with increased risk of acute hospitalizations, particularly for those taking >10 medications. There are two likely drivers for these effects: PP as a contributing cause of an increased drug-related toxicity or PP as an indicator of greater comorbidity burden. It is unclear in what manner PP influences adverse outcomes and our data suggest the risk may be non linear. However, PP should undoubtedly be closely monitored to minimize potentially inappropriate combination of prescribed medications. These observations also support the hypothesis that polypharmacy may be a useful clinical tool: a simple, novel and readily measurable predictor of clinical outcomes. Undoubtedly, more research and further validation studies need to be done before firm conclusions can be made. However, patients exposed to higher levels of polypharmacy represent a population of particular relevance to the modern NHS: these patients are typically excluded from clinical trials and therefore data regarding drug efficacy in the setting of polypharmacy are lacking (27).

Acknowledgement: This study was supported by an Arthritis Research UK Experimental Arthritis Treatment Centre grant and project of the MHCR for conceptual research development No. 023728.

References

1. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med* 2015;13:74
2. Treharne GJ, Douglas KM, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. *Musculoskeletal Care* 2007;5:175-90
3. Gabriel SE. Why do people with rheumatoid arthritis still die prematurely? *Annals of the rheumatic diseases* 2008;67 Suppl 3:iii30-4
4. Gullick NJ, Scott DL. Co-morbidities in established rheumatoid arthritis. *Best practice & research Clinical rheumatology* 2011;25:469-83
5. Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Annals of the rheumatic diseases* 2014;73:62-8
6. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Arthritis and rheumatism* 2008;59:1690-7
7. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* 2011;50:124-31
8. Mercer LK, Davies R, Galloway JB, Low A, Lunt M, Dixon WG, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. *Rheumatology* 2013;52:91-8
9. Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. *Annals of the rheumatic diseases* 2010;69:1920-5
10. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf* 2010;19:901-10
11. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9
12. Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D, et al. Ten-year trends in hospital admissions for adverse drug reactions in England 1999-2009. *J R Soc Med* 2010;103:239-50
13. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200-5
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Annals of the rheumatic diseases* 2010;69:1580-8
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and rheumatism* 1988;31:315-24
16. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255-9
17. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc* 2015;
18. Lea M, Rognan SE, Koristovic R, Wyller TB, Molden E. Severity and management of drug-drug interactions in acute geriatric patients. *Drugs Aging* 2013;30:721-7
19. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015;44:213-8

20. Hallas J, Harvald B, Gram LF, Grodum E, Brosen K, Haghfelt T, et al. Drug related hospital admissions: the role of definitions and intensity of data collection, and the possibility of prevention. *J Intern Med* 1990;228:83-90
21. Scott IA, Hilmer SN, Reeve E, Potter K, Le Couteur D, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015;175:827-34
22. Vyas A, Pan X, Sambamoorthi U. Chronic Condition Clusters and Polypharmacy among Adults. *Int J Family Med* 2012;2012:193168
23. Hippisley-Cox J, Coupland C. Predicting risk of emergency admission to hospital using primary care data: derivation and validation of QAdmissions score. *BMJ Open* 2013;3:e003482
24. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PloS one* 2009;4:e4439
25. Patel H, Bell D, Molokhia M, Srishanmuganathan J, Patel M, Car J, et al. Trends in hospital admissions for adverse drug reactions in England: analysis of national hospital episode statistics 1998-2005. *BMC Clin Pharmacol* 2007;7:9
26. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. *British journal of clinical pharmacology* 2014;77:1073-82
27. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ* 2015;350:h1059
28. Yurkovich M, Avina-Zubieta JA, Thomas J, Gorenchtein M, Lacaille D. A systematic review identifies valid comorbidity indices derived from administrative health data. *J Clin Epidemiol* 2015;68:3-14
29. Donnan PT, Dorward DW, Mutch B, Morris AD. Development and validation of a model for predicting emergency admissions over the next year (PEONY): a UK historical cohort study. *Arch Intern Med* 2008;168:1416-22

Tables

Table 1 Characteristic and prescription strategy among RA patients involved in the study

** Mantel-Haenszel test for trend*

Abbreviations: DAS28, disease activity score; HAQ, Health Assessment Questionnaire; DMARDs, Disease Modifying Antirheumatic Drugs; SD, standard deviation

Table 2 Association between polypharmacy and first acute hospitalization in RA patients over 18 months observation period

** Proportional hazards assumptions confirmed using Nelson-Aalen plots and Schoenfeld residuals*

Abbreviations: HR, hazard ratio; CI, confidence interval; DAS28, disease activity score

Table 3 Analysis of relationship between adverse drug reaction (ADR) and first acute hospitalization, implicated drug-drug interactions and avoidability of such events in all RA patients.

NA, not applicable

Table 4 Analysis of relationship between adverse drug reaction (ADR) and first acute hospitalization, implicated drug-drug interactions and avoidability of such events in RA patients across polypharmacy strata.

** calculated from definitely+probably+possibly ADR related admissions*

Supplementary table 1 Association between different treatment strategies and first acute hospitalisation risk in RA patients

Abbreviations: HR, hazard ratio; CI, confidence interval; DMARD, disease-modifying antirheumatic drug

Supplementary table 2 The proportion of drugs for treatment of rheumatoid arthritis associated with infection-related admissions.

Abbreviations: DMARD, disease-modifying antirheumatic drug; NA, not applicable

Legend to figures

Figure 1 Association between the number of medications and DAS28 (a), HAQ (b), age (c) and disease duration (d).

Figure 2 Increasing polypharmacy was associated with more frequent acute hospitalisations with a marked non-linear increase in risk in patients taking ≥ 10 medications.

Supplementary figure 1 Baseline prescription of non-RA drugs in RA population (a). Causes of the first hospitalization in RA population (b).

Figure 1

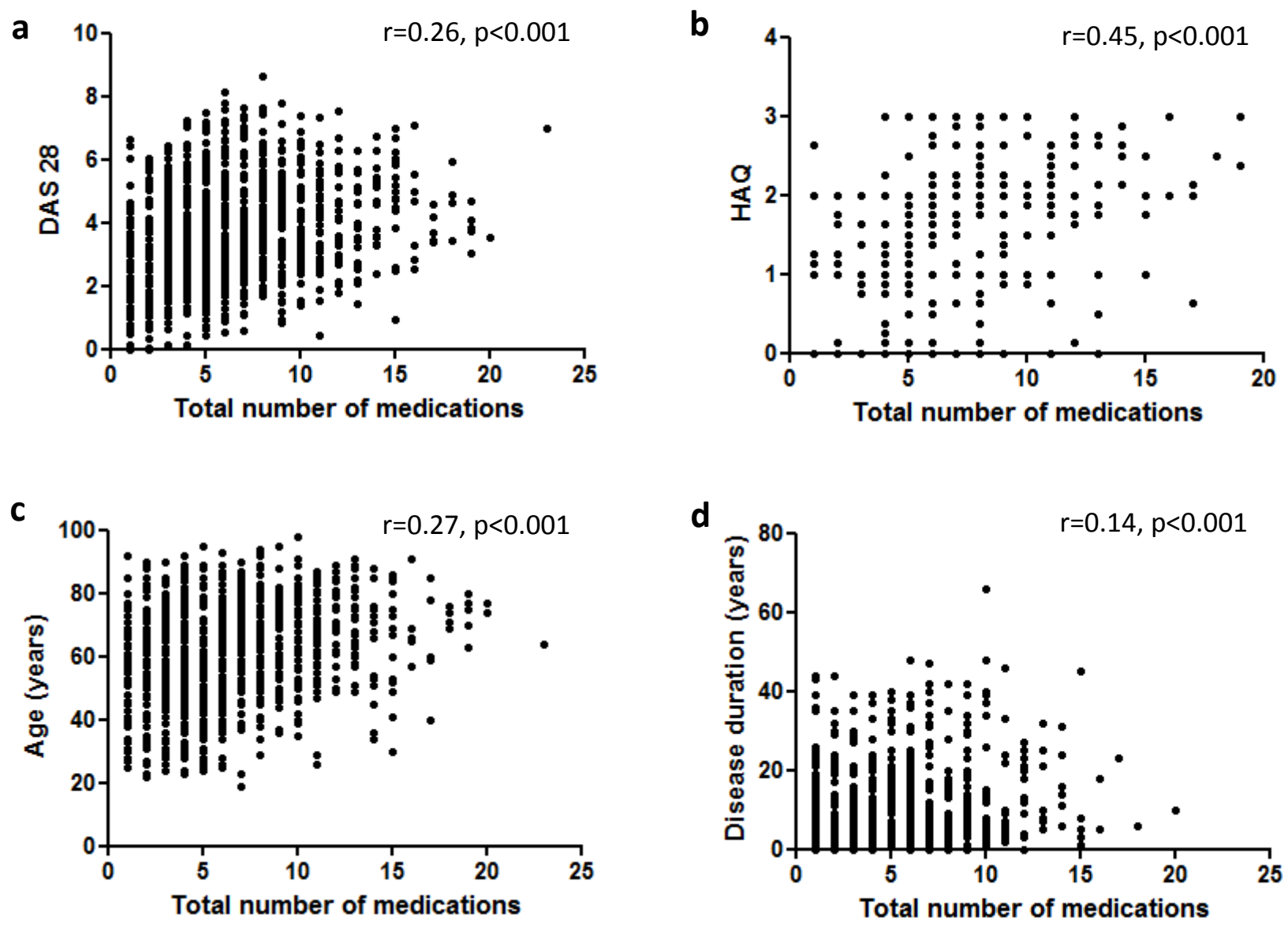
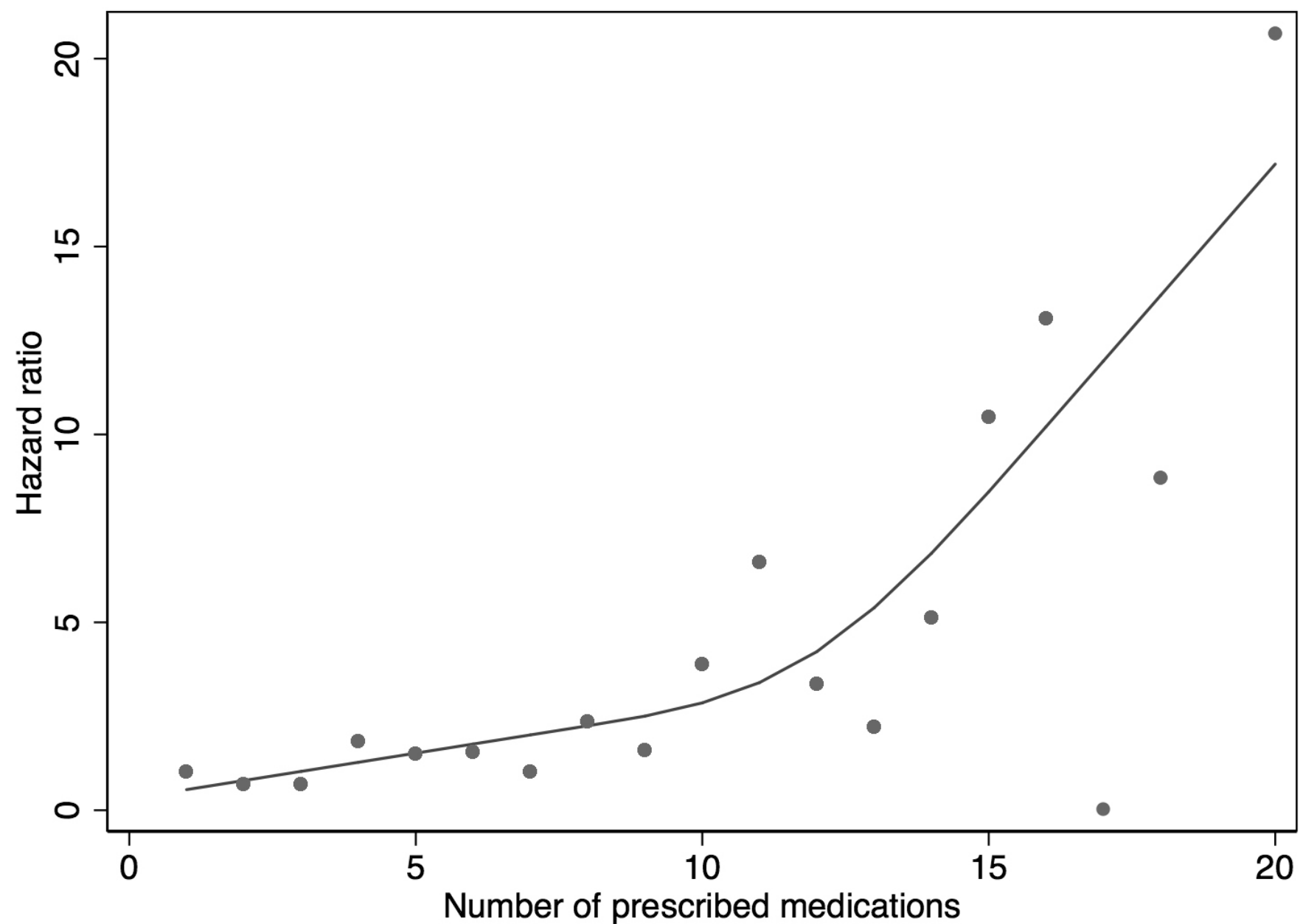
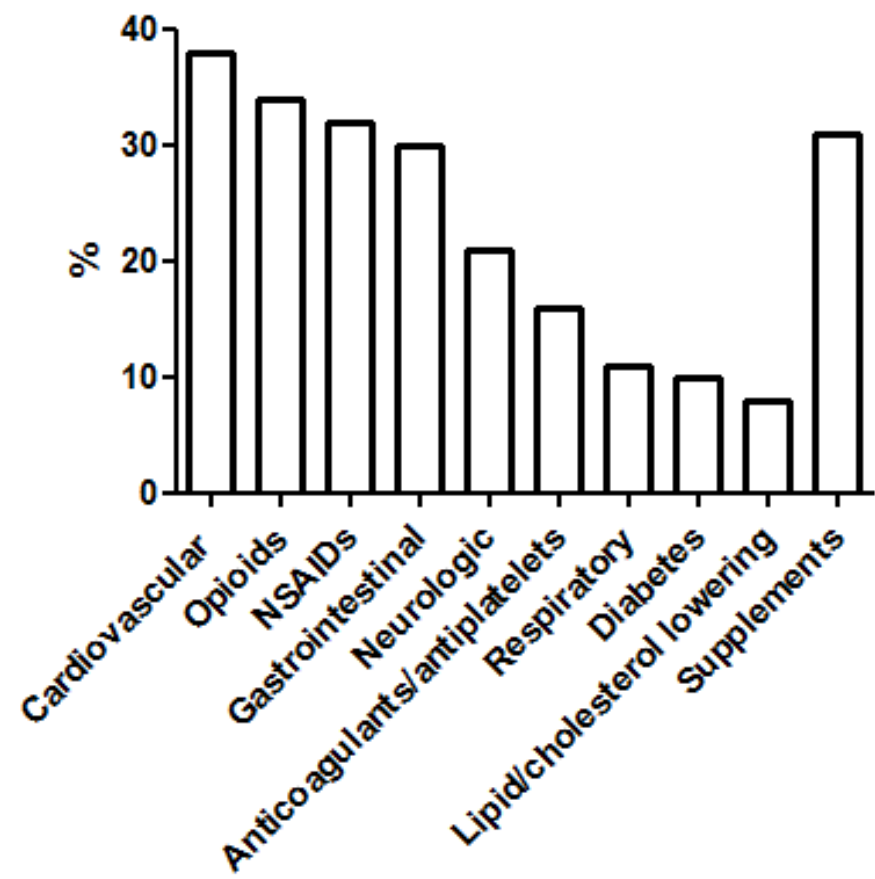


Figure 2

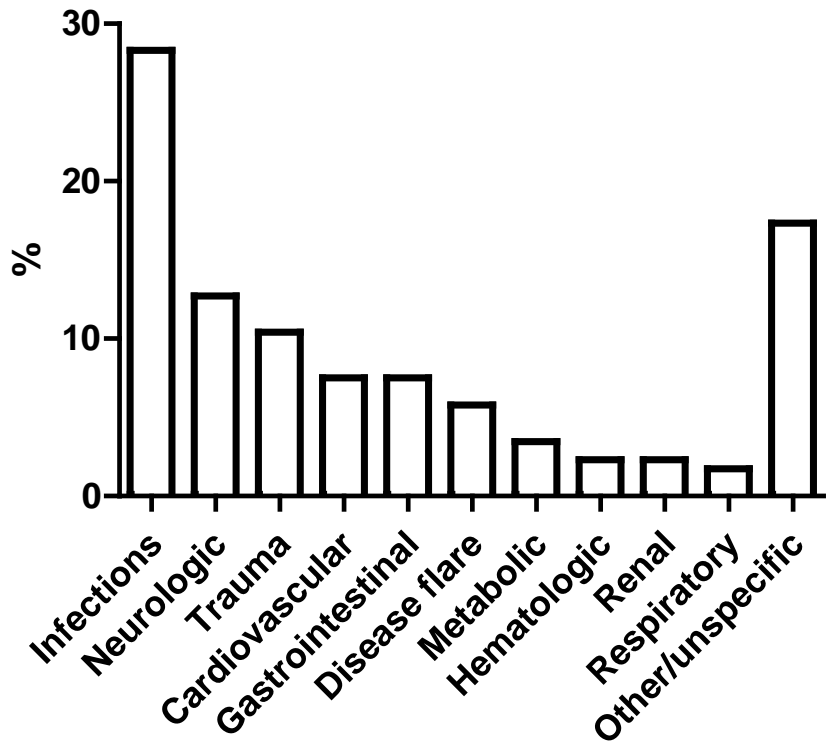


Supplementary figure

a



b



Supplementary table 2

ADR related admissions	definite	probable	possible	unlikely
N	1	3	39	7
RA drug definitely implicated, N	1	3	33	NA
Corticosteroid implicated	0	0	5	
DMARD implicated	1	2	25	
Biologic implicated	0	3	8	